HuGE Fact Sheet

Androgen Receptor Gene and Prostate Cancer

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PUBLISHED: May 2002

AR Gene

The androgen receptor (*AR*) gene is located in the Xq11.2–q12 chromosome and consists of eight exons. This gene is a member of the steroid/nuclear receptor gene superfamily. There are two domains that are directly responsible for the transactivation activity of the AR protein. Of these domains, the ligand-independent AF-1 is encoded within exon 1.

Prevalence Of Gene Variants

There are three known *AR* gene polymorphisms: the (CAG)n trinucleotide repeat, the (GGC)n trinucleotide repeat, and the R726L single nucleotide polymorphism (1). Studies have suggested that twenty-seven alleles ranging from 5 to 31 repeats were observed in various populations. Short CAG repeats (less than or equal to 22 repeats) were found to be more prevalent in African-American males who are at high risk for prostate cancer and less prevalent in Asians who are at lower risk for this disease (2). This observation reveals that variation in androgen receptor CAG repeat length differs considerably among human populations. African Americans have the lowest frequency (20%) of the GGC allele with 16 repeats; the comparable values for intermediate-risk whites were 57% and low-risk Asians were 70% (2).

Disease Burden

In recent years, prostate cancer has become the most common cancer and the second leading cause of cancer death in men in the United States. There is a 65-fold difference in incidence of prostate cancer between the populations with the highest (African-American) and lowest (Asian) risk (3). Compared with rates of prostate cancer in the United States, rates are slightly lower in some countries of Western Europe such as Denmark, United Kingdom, Italy, and Spain. In Asia, prostate cancer rates in Singapore, Hong Kong, and Bombay are less than half of those in Israel (4).

Consistent with the interracial variation in CAG and GGC distributions, there was an excess among white patients with fewer than 22 CAG and not-16 GGC repeats relative to white controls (relative risk, 2.1; one-sided P = 0.08) (2). No linkage disequilibrium was observed between the two numbers of CAG and GGC repeats among unaffected subjects. However, there was a statistically significant negative association between the numbers of CAG and GGC repeats among the prostate cancer patients studied (two-sided P = 0.008). The (CAG)n repeat was found to play a role in predisposition to prostate cancer. In one of the case-control studies conducted in Australia, the odds ratio of prostate carcinoma for a change of 5 CAG repeats was 0.98 (95% confidence interval, 0.84-1.15); therefore, investigators concluded that the *AR* CAG repeat polymorphism was not a risk factor for prostate carcinoma. However, in this study, a shorter repeat sequence was found to be associated with earlier age at diagnosis (5) .

In another study conducted in China, Chinese men have been found to have longer CAG (equal or longer than 23) repeats compared with western men. Another finding of this study suggests that even in a very low-risk population, a shorter CAG repeat length confers a higher risk of clinically significant prostate cancer. Chinese men with a CAG repeat length shorter than 23 (median length) had a 65% increased risk of prostate cancer (odds ratio, 1.65; 95% confidence interval, 1.14-2.39) (6). Finally, according to the study by Miller et al., the (CAG)n and (GGN)n repeats do not play a major role in familial prostate cancer (7).

Interactions
Studies show a two-fold increase in relative risk for combination of CAG and GGN short repeats (less or equal to 22). The AR, by transactivating some genes, might influence prostate cancer risk through several pathways. Other genes can directly or indirectly activate the AR, augmenting prostate cancer risk. For instance, HSD17B3, the gene that encodes 17 b -hydroxysteroid dehydrogenase type III, the testicular 17-ketoreductase, favors the reduction of androstenedione to testosterone in the testis and can indirectly (through dihydrotestosterone) activate AR.

In the study by Xue et al. (8), men who carry a short *AR* CAG (less or equal to 22) allele and who also carry two copies of the PSA G allele, had a nearly 3-fold increase in risk of advanced prostate cancer; however, the limitation of this study was a small sample size, and results need to be replicated before they can be considered conclusive.

The study by Yeh et al. (9) suggests that the BRCA1 may function as an AR coregulator and play positive roles in androgen-induced cell death in prostate cancer cells and other androgen/AR target organs. BRCA1 has been identified by linkage studies with a familial history of prostate cancer in addition to breast and ovarian cancer. Struewing et al. reported a risk of prostate cancer of up to 25% by the age of 70 years for carriers of any of the two BRCA1 mutations, whereas the risk was only 5% for carriers of the BRCA2 mutation and 3.8% for those who were not carriers (10).

There is strong evidence that environmental factors can influence the risk of prostate cancer: The wide variation in disease incidence observed worldwide, the observation that prostate cancer rates among immigrants tend to approach those of the host country, and results from studies such as the Physicians' Health Study that showed that men who consumed at least two and a half servings of dairy foods daily were about 30% more likely to develop prostate cancer than men who consume only half a serving per day. No studies have examined the interaction between specific environmental risk factors for prostate cancer and the *AR* gene.

Larger studies are needed to evaluate the combined effect of CAG and GGN repeats. Because gene-gene and gene-environment interactions may potentially contribute to prostate cancer risk, it would be desirable to conduct studies in which both biomarkers (or other measures) of exposure and polymorphism of multiple genes are examined.

Laboratory Tests
CAG and GGC genotypes were assayed by separating radioactively labeled polymerase chain reaction (PCR) products on polyacrylamide gels. In addition, automated sequencing systems have been used to assay these polymorphisms.

Population Testing
No laboratory tests are available to the general public for AR gene diagnostic purposes.

References

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Web Sites

1. Fred Hutchinson Cancer Research Center
2. National Cancer Institute - Prostate Cancer Home Page
3. National Cancer Institute - Planning for Prostate Cancer Research
4. National Cancer Institute - The Surveillance, Epidemiology, and End Results (SEER) Program
5. British Columbia Cancer Research Center
6. The National Cancer Institute of Canada
7. American Cancer Society